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The Implications of Sarcopenia and Sarcopenic Obesity on Cardiometabolic Disease

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ABSTRACT

The important changes in body composition associated with aging are a decline in skeletal muscle mass and an increase in body fat. Body fat distribution also changes with age; subcutaneous fat decreases and visceral abdominal fat increase, which contributes to numerous cardiometabolic diseases (CMDs) such as type 2 diabetes, dyslipidemia, and cardiovascular disease (CVD). Sarcopenia often accompanied by an increase in body fat and vice versa, a scenario termed sarcopenic obesity (SO), which might lead to the cumulative risk of both sarcopenia and obesity. However, there is still no consensus regarding the definition and consequences of SO. The lack of a unified definition for SO might contribute to inconsistent findings about the association of SO with CMD. Complex etiologies are associated with development of SO. A vicious cycle between the loss of muscle and the accumulation of ectopic fat might be associated with CMD via an intricate interplay of factors including proinflammatory cytokines, oxidative stress, mitochondrial dysfunction, insulin resistance, dietary energy, physical activity, mitochondrial dysfunction, and other factors that have yet to be identified. Moreover, recent epidemiological studies suggest that SO is related to CVD and mortality. This review focuses on the current literature with regard to the association between sarcopenia, dynapenia, and obesity, as well as their implications for CMD. The ultimate goal of this *Prospects* is to encourage conduct of well-designed future studies that elucidate the relationship among sarcopenia, SO, and CMD. J. Cell. Biochem. 116: 1171–1178, 2015.

KEY WORDS: SARCOPENIC OBESITY; CARDIOMETABOLIC DISEASE; SARCOPENIA; VISCERAL OBESITY

INTRODUCTION

Over the past decade, the prevalence of obesity and sarcopenia has exploded in the aging society. Obesity and age-related muscle loss were once thought to be mutually exclusive as were obesity and osteoporosis [Rosen and Bouxsein, 2006]. In other words, obese individuals are considered to have a larger skeletal muscle mass than lean subjects of the same age and gender. In addition, there is a positive correlation between body mass index (BMI), a simple index of obesity, and muscle mass because a heavier body weight might provide mechanical load and stimuli for a higher accrual of muscle mass [Morse and Soeldner, 1964]. Despite these findings, recent studies revealed that obesity might be associated with a low muscle mass. Moreover, some obese individuals have a lower muscle mass or muscle to fat ratio, a scenario termed sarcopenic obesity (SO). These individuals might have an additional or synergistic risk derived from both sarcopenia and obesity. Obesity increases for itself the risk of significant cardiometabolic diseases (CMDs) such a type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease (CVD). In addition, low muscle mass or sarcopenia might increase these risks further.

CVD is a major cause of disability and premature mortality worldwide. Moreover, the prevalence of CVD increases dramatically with age, and CVD represents the main cause of mortality in the aged population. Obesity is a significant risk factor for CMD, but the effects of increasing BMI on mortality are less pronounced in the elderly than in middle-aged adults. In addition, several investigators have reported that the percentage of body fat

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increases in the elderly compared to young adults, regardless of BMI. Therefore, BMI might not be a good measure of general adiposity in old age, which could lead to wrong estimates of obesity-related health risks such as CMD. Therefore, the analysis of body composition (fat mass and fat-free mass) might be a better risk predictor than BMI in these individuals.

The most dramatic age-related changes in body composition are a decrease in muscle mass and an increase in fat mass. With the coining of the term sarcopenia, muscle mass has been a major focus of aging research over the past 25 years [Janssen, 2010]. The motivating idea behind this is that physical disability and metabolic abnormalities might be determined by skeletal muscle mass. Therefore, a logical strategy to prevent disability and metabolic disease is to slow or reverse age-related decreases in muscle mass. However, previous studies have shown that the link between lean mass, functional performance, and strength is not particularly strong [Clark and Manini, 2010]. The degree of functional improvement is correlated with the extent of adipose tissue loss, regardless of increasing muscle mass. In addition, CMD cannot be predicted using only muscle mass [Stephen and Janssen, 2009]. Therefore, concepts that combine low muscle quantity (and/or quality) and high body fat are required as stronger predictors of physical disability and CVD risk compared to either low muscle mass or obesity alone.

A reduced muscle mass is associated with the accumulation of visceral fat. Although many explanations for SO have been proposed, several lines of evidence suggest that a vicious circle between the loss of muscle mass and increased fat mass is the mainstay of SO development. Less muscle mass reduces total energy expenditure, and might lead to visceral obesity. In contrast, accumulated visceral fat induces chronic inflammation, which contributes to the development and progression of sarcopenia. Here, we reviewed the mechanisms of SO in terms of the link between muscle and fat. In addition, we updated the present clinical and experimental observations regarding the potential mechanisms underlying the association between SO and CMD. Expanding our understanding of the concepts and complex etiologies of SO might help elucidate the relationship between CVD and SO and identify potential therapeutic targets that delay the progress from sarcopenia and obesity to CMD in the rapidly aging society.

PATHOPHYSIOLOGY OF SARCOPENIC OBESITY AND CARDIOMETABOLIC DISEASE

RELATIONSHIP BETWEEN MUSCLE FAT, INSULIN RESISTANCE, AND ATHEROSCLEROSIS

Histologically, SO presents as type II muscle fiber atrophy and the infiltration of muscle tissue components by an increased frequency of adipocytes or lipid deposition within muscle fibers [Kraegen and Cooney, 2008; Sakuma and Yamaguchi, 2013]. In terms of adipocytes within muscle, it has been suggested that muscle satellite cells in culture are capable of forming adipocytes and myocytes [Asakura et al., 2001]. In humans, muscle satellite cells can acquire features of adipocytes, which might explain the presence of mature adipocytes within skeletal muscle [Vettor et al., 2009; Thornell, 2011]. This occurs under some pathological conditions such as obesity, hyperglycemia, and the presence of high concentrations of plasma fatty acids, as well as a sedentary lifestyle or aging [Vettor et al., 2009]. In addition, insulin resistance has been correlated with muscle lipid accumulation in many animal studies [Kraegen and Cooney, 2008]. A number of studies in human have suggested that intramyocellular triglyceride (IMTG) are an important correlate of skeletal muscle insulin resistance, although active lipid intermediates such as long chain fatty acid coenzyme As, diacylgycerol, and ceramides might induce lipid-induced muscle insulin resistance rather than IMTG [Kraegen and Cooney, 2008]. The AMP-activated protein kinase (AMPK) pathway also plays a key role in regulating tissue energy metabolism. In addition, activation of this pathway leads to reduced IMTG, and decreases ceramide synthesis, fatty acid-induced nuclear factor -κB (NF-κB) activation, and mammalian target of rapamycin (mTOR) activity, all of which can induce insulin resistance [Kraegen and Cooney, 2008]. Thus, dysregulated AMPK pathway, which occurs in certain disease states or conditions (Aging, obesity, metabolic syndrome, and CVD) might contribute to fat accumulation and insulin resistance in skeletal muscle, which subsequently worsens SO. Moreover, middle-aged subjects with diabetes who had more muscle fat and visceral fat, higher insulin resistance, and a reduced mid-thigh normal density muscle area had greater carotid intima-media thickness than healthy control [Kim et al., 2010a]. Therefore, the vicious cycle between the loss of muscle and the accumulation of ectopic fat might be associated with atherosclerosis via a complex interplay of factors, including proinflammatory cytokines, increasing insulin resistance, dietary energy, physical activity, oxidative stress, mitochondrial dysfunction, and other factors that have yet to be identified (Fig. 1).

VICIOUS CYCLE OF SO

Dose obesity cause so as a risk factor for CMD? Obesity and sarcopenia might be strongly interconnected pathogenically. First, obesity is associated with increased concentration of pro-inflammatory cytokines, which can stimulate the transition from obesity to developing CVD and SO. Increased circulating levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 (IL-1), and C-reactive protein (CRP) have been reported in subjects with SO. Adipose tissue is an active endocrine organ that secretes hormones and cytokines that affect systemic inflammatory status [Schrager et al., 2007; Kim et al., 2013a]. Adipocytes or infiltrating macrophages in adipose tissue produce adipokines and proinflammatory cytokines, such as IL-6 and TNF-α, which induce the production of CRP in the liver. These inflammatory cytokines influence skeletal muscle negatively via catabolic effects. Along with the increased levels of these adipokines in adipose tissue, the reduced secretion of adiponectin contributes to local and systemic low-grade chronic inflammation [Tilg and Moschen, 2006]. Adiponectin stimulates fatty acid oxidation and glucose uptake in skeletal muscle and adipose tissue, which are dependent on AMPK signaling [Wu et al., 2003]. Adiponectin activates AMPK, increases the production of anti-inflammatory cytokines, and inhibits NF-kB signaling, thereby decreasing the production of TNF-α [Sakuma and Yamaguchi, 2013]. In contrast, serum levels of leptin increase with adipose tissue mass. Increased circulating levels of leptin are

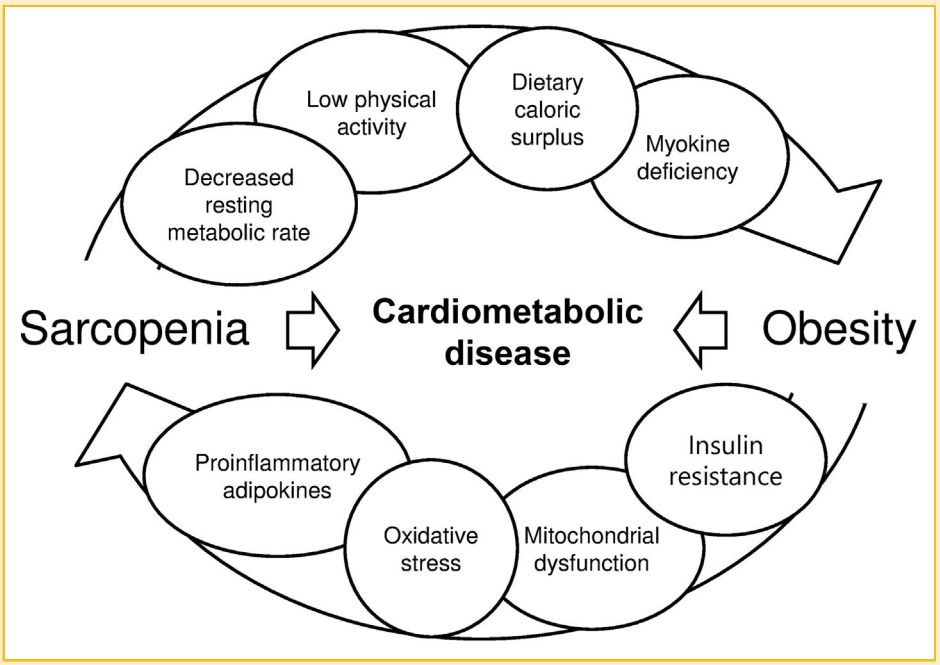

Fig. 1. Theoretical relationships between vicious cycle of sarcopenia and obesity and CMD.

independently associated with insulin resistance and metabolic syndrome in humans [Martin et al., 2008]. In addition, leptin receptors are down-regulated by leptin itself or insulin resistance. Plasma levels of leptin are highest in individuals with SO followed by simple obesity, even after adjusting for age and body weight [Kohara et al., 2011]. These findings suggest that leptin might play an important role in the development of SO, and might also link SO with CMD. Adipocyte fatty acid-binding protein (A-FABP), a novel adipokine, also plays a key role in obesity-related insulin resistance and inflammation, which might be involved in the pathogenesis of SO and CMD. Kim et al. reported that serum A-FABP levels are associated with visceral fat positively and muscle mass index negatively [Kim et al., 2013b]. In addition, multiple logistic regression analysis showed that the presence of SO was independently associated with increased serum levels of adipocyte fatty acid-binding protein [Kim et al., 2013b]. Therefore, low-grade inflammation via adipokines might be a principal mechanism behind the vicious cycle of SO and CMD.

Excess caloric intake that results in obesity might also accelerate sarcopenia by causing high levels of oxidative stress. The excessive intake of high-calorie, rapidly digestible food leads to abnormal surges in serum free fatty acids and glucose levels, which are linked to the increased generation of reactive oxygen species [O′Keefe and Bell, 2007]. Thus, the repeated consumption of high-calorie meals might not only exacerbate obesity, but may also induce oxidative damage to myocytes in skeletal muscle. Unlikely excessive caloric intake, calorie restriction attenuates sarcopenia by reducing the incidence of mitochondrial abnormalities and attenuating oxidative stress, although excessive calorie restriction in humans is accompanied by many adverse effects such as weakness, osteoporosis, and depression [Marzetti et al., 2009]. Although more studies are needed, oxidative stress caused by the excessive intake of high-calorie meals might contribute to obesity-related comorbidities, including SO and CMD.

Dose sarcopenia cause SO and increase the cardiovascular risk? The loss of muscle mass might also facilitate obesity and insulin resistance. The metabolic effects of sarcopenia, including a decreased resting metabolic rate and reduced physical activity, might lead to an increased fat mass and particularly visceral fat to cause insulin resistance, CMD, and increased CMD related morbidities and mortality [Dominguez and Barbagallo, 2007]. We observed that sarcopenia is independently associated with type 2 diabetes and non-alcoholic fatty liver disease (NAFLD), which are known as important risk factors for CVD, in Korean Sarcopenic Obesity Study (KSOS) [Kim et al., 2010b; Hong et al., 2014].

Physical inactivity is an important risk factor for obesity and sarcopenia. In contrast, exercise training is one of the safest, most inexpensive, and most feasible therapeutic interventions to prevent the age-related loss of muscle mass and/or strength, as well as obesity. Resistance training offers a wide range of physiological benefits to skeletal muscle, including reduced inflammation, increased mitochondrial function, and satellite cell activity. Moreover, aerobic exercise conserves muscle mass by improving muscle blood flow and decreasing oxidative stress [Buford et al., 2010]. Davidson et al. randomized elderly obese subjects into four groups: a control group, a resistance training group, an aerobic exercise group, and a combined resistance and aerobic exercise group [Davidson et al., 2009]. Insulin resistance improved in the aerobic and combined exercise group, although it did not change in the resistance training group. In addition, visceral fat decreased and

endurance capacity improved in the aerobic and combined exercise group, whereas skeletal muscle mass and muscle strength were enhanced in the resistance and combined exercise group [Davidson et al., 2009]. These results suggest that combination of resistance and aerobic exercise might be the optimal strategy for simultaneously improving visceral obesity and sarcopenia, which ameliorates metabolic complications such as CMD and functional limitations in the elderly. In addition, regular physical activity improves cardiorespiratory fitness levels, which is considered one of the most modifiable CVD risk parameters, and plays a role in the prevention of CVD [Church et al., 2007]. Recent observational studies have suggested that low physical activity and cardiorespiratory fitness are associated with an increased risk of sarcopenia and SO [Kim et al., 2014]. Moreover, the Cardiovascular Health Study, a large longitudinal study, showed that the increased risk of CVD associated with SO decreased from 23 to 18% after controlling for physical activity [Stephen and Janssen, 2009]. This result suggests that physical activity might be a good therapeutic interventions to interrupt the link between SO and CMD.

Skeletal muscle is a primary tissue responsible for insulin-mediated glucose disposal. Thus, the loss of skeletal muscle as the largest insulin-sensitive tissue might cause insulin resistance, which promotes CMD. Like adipose tissue, skeletal muscle was recently established as an endocrine organ that secretes hormone-like factors to modulate systemic metabolism. Analogous to the adipokines, muscle-derived proteins are called myokines. Apart from adiponectin, most adipokines have proinflammatory properties that cause the development of obesity-related CMD, whereas myokines could counteract the harmful effects of adipokines [Pedersen and Febbraio, 2012]. The first muscle-derived secreted protein to be described was cytokine interleukin-6 (IL-6). It is now clear that many additional signaling molecules are produced by contracting muscle fibers: the current list of myokines includes IL-6, IL-8, IL-15, brain-derived neurotrophic factor (BDNF), leukemia inhibitory factor (LIF), follistatin-like 1, and fibroblast growth factor-21 (FGF-21). Myokines function via autocrine, paracrine, and endocrine manners, and thereby have major implications on the metabolic and other properties of muscle. IL-6 induces glucose uptake and fatty acid β-oxidation in muscle, stimulates hepatic gluconeogenesis, and induces lipolysis in adipose tissue. Similarly, IL-15 is involved in the crosstalk between muscle and adipose tissue by decreasing the mass of white adipose tissue. High local concentrations of IL-8 might be involved in exercise-induced angiogenesis, and hence, the increased capillarization of skeletal muscle. Böstrom et al. demonstrated that the overexpression of PPAR-gamma co-activator-1 alpha (PGC1-α) in the muscles of mice stimulated an increase in expression of FNDC5, a membrane protein that is cleaved and secreted as the novel myokine, irisin [Bostrom et al., 2012]. Exercise increases the circulating levels of irisin in mice and humans. Furthermore, increased irisin levels activate thermogenesis by inducing the browning of white adipose tissue, thereby improving obesity and glucose homeostasis [Bostrom et al., 2012]. These results support the concept that skeletal muscle exerts beneficial effects on CMD via circulating mediators such as myokines, which play a pivotal role in the crosstalk between muscle and adipose tissue. Thus, taken together, the vicious circle between muscle loss and fat gain might lead to more severe sarcopenia or obesity via changes in body composition and increases in the risk factors for CMD, which in turn increase the risk of CVD-related events.

RELATIONSHIP BETWEEN CMD AND BODY COMPOSITION PHENOTYPES: CLINICAL OBSERVATIONS

CMD AND ABDOMINAL OBESITY

Visceral adipose tissue contributes to CVD, although the causal relationship between obesity and CVD are controversial. Several studies have demonstrated that visceral adipose tissue might cause CVD by affecting insulin resistance, glucose and lipid metabolism, coagulation, and inflammation [Despres and Lemieux, 2006]. In addition, several cross-sectional studies have revealed that patients with subclinical or overt CVD have greater visceral adipose tissue that those without, even after adjusting for potential confounders [Marques et al., 2010]. Consistent with this, several prospective studies have demonstrated that visceral adiposity is independently associated with the incidence of CVD after adjusting for clinical risk factors and generalized adiposity [Britton et al., 2013]. These findings support the hypothesis that abdominal obesity might be a better predictor of CMD than BMI.

CMD AND LOW MUSCLE MASS OR SARCOPENIA

Sarcopenia or low muscle mass is related to functional impairment and physical disability, and is associated with an increased risk of mortality [Han et al., 2010]. Recent studies have focused on potential effect of low muscle mass or sarcopenia on cardiometabolic disorders. As noted above, the cellular and molecular mechanism responsible for sarcopenia, such as oxidative stress, inflammation, and insulin resistance are associated with CVD [Kim and Choi, 2013]. Clinical observational studies have demonstrated that low muscle mass is associated with arterial stiffness, which is an independent predictor of CVD [Abbatecola et al., 2012]. A prospective observational cohort study demonstrated that a low thigh circumference was associated with an increased risk of CVD and total mortality in both males and females [Heitmann and Frederiksen, 2009]. On the other hand, muscle strength is also associated with all-cause and CVD mortality in the aged population [Sasaki et al., 2007]. As a strong risk factor for CVD, low muscle mass or strength might be as important as obesity although more research is needed to clarify the relative importance of sarcopenia and obesity on the risk of CVD.

CMD AND SO

Since obesity, particularly visceral abdominal fat, and low muscle mass or sarcopenia both predict CMD risk, it is possible that the combination of obesity and sarcopenia might be associated with a greater risk of CMD.

Cross-sectional studies Several cross-sectional studies have revealed that SO is associated with surrogate markers for CVD and mortality [Honda et al., 2007]. Schrager et al. demonstrated that

obesity indices such as BMI and waist circumference are positively associated, whereas muscle strength is negatively associated with circulating levels of proinflammatory cytokines [Schrager et al., 2007]. This study defined sarcopenia as lowest tertile of muscle strength, and stated that SO was associated with high circulating levels of inflammatory markers, which are recognized risk factors of CVD. In addition, Honda et al. showed that SO was associated with inflammation and increased mortality in patients with end-stage renal disease [Honda et al., 2007]. In support of the effects of SO on CMD, several large Asian cohort studies investigated the relationship between SO and metabolic syndrome [Kim et al., 2009; Lim et al., 2010b]. SO female subjects, who were defined using total skeletal muscle mass adjusted by weight, had three times the risk of metabolic syndrome whereas subjects with obesity only had approximately twice the risk of metabolic syndrome as normal subjects [Kim et al., 2009]. Similar trends were observed in males in the KSOS [Kim et al., 2009]. This question was also examined in the Korean Longitudinal Study on Health and Aging (KLoSHA). Participants with SO were eight times as likely to develop metabolic syndrome compared to obese or sarcopenic subjects when SO was classified using appendicular skeletal muscle mass adjusted by weight as an index of sarcopenia and visceral fat area as an index of obesity [Lim et al., 2010b]. However, Aubertin-Leheudre and colleagues reported that SO was linked to a lower risk of CMD [Aubertin-Leheudre et al., 2006]. Obese postmenopausal females had significantly more abdominal fat mass and a worse lipid profile than those with SO [Aubertin-Leheudre et al., 2006]. Although these inconsistent findings might reflect the heterogeneity in the methods to assess sarcopenia and obesity as well as study population, several studies using the fat and muscle mass ratio as a surrogate index of SO showed a consistent positive association between SO and CMD risks [Lim et al., 2010a; Kim et al., 2011; Prado et al., 2012]. SO that is characterized by a high fat mass and low muscle mass might reflect a high metabolic load and low metabolic capacity, which leads to metabolic syndrome and arterial stiffness [Kim et al., 2011; Lim et al., 2010a; Prado et al., 2012].

Prospective studies Prospective studies have also shown consistent associations between SO and mortality risk, although the association was mostly evaluated in disease-specific populations [Prado et al., 2008; Tan et al., 2009]. However, the effect of SO on CVD outcomes and mortality has been poorly studied. A large prospective study showed that SO defined using waist circumference and muscle strength was associated with an increased risk of CVD [Stephen and Janssen, 2009]. In contrast, longitudinal data from the New Mexico Aging Process Study reported that the prevalence of metabolic syndrome was greatest in nonsarcopenic obese subjects, followed by SO individuals; it was lowest in the sarcopenic group, as defined by appendicular skeletal muscle mass adjusted by height squared [Baumgartner et al., 2004]. This finding was similar to the results of a small cross-sectional study of 22 obese postmenopausal female [Aubertin-Leheudre et al., 2006]. Recently, prospective cohort data from older male in the British Regional Heart Study demonstrated that sarcopenia (mid-arm muscle circumference), central obesity (waist circumference), and SO were associated with increased CVD mortality, although the greater risk in men with SO was no longer significant after adjusting for lifestyle variables [Atkins et al., 2014].

CRITICAL ISSUES IN STUDIES OF THE ASSOCIATION BETWEEN SO AND CMD

A NEED FOR A STANDARIZED DIAGNOSTIC APPROACHES

As mentioned above, studies that analyzed the association between SO and CMD showed inconsistent findings, which might be caused by the lack of standardized diagnostic methods. Prado et al. stated that the heterogeneities among studies could be categorized into seven appraisals: body composition method, cut-off points for the classification of sarcopenia and obesity, adjustment (height^2 vs. weight), agreement (bioimpedence analysis-derived prediction equations vs. duel energy X-ray absorptiometry), study design, biological validity, and risk prediction [Prado et al., 2012]. Among these, although all were important to obtain a standard definition of SO, the adjustment of muscle quantity appeared to have more of an impact on discrepancies regarding the association between SO and CMD. Regarding the definition used for sarcopenia, adjustment for height squared has been more preferred method than body weight [Kim et al., 2009; Lim et al., 2010b; Kohara et al., 2011]. However, when muscle mass or area was adjusted for body weight, subjects with SO were more insulin resistant and at a higher risk of developing CMD than those with either sarcopenia or obesity alone. Moreover, muscle mass adjusted for weight was negatively correlated with BMI, visceral fat area, and the homostasis model assessment of insulin resistance whereas muscle mass adjusted by height squared was positively associated with these CMD risk factors [Lim et al., 2010b]. Furthermore, several prospective studies that used muscle mass adjusted by height squared to define SO revealed no significant difference in risk of outcomes such as CVD events and mortality between sarcopenic, obese, or SO groups and the normal reference group [Stephen and Janssen, 2009; Atkins et al., 2014]. In contrast, sarcopenia and abdominal obesity classified using mid-thigh muscle area and waist circumference were associated with all-cause mortality, with highest risk in males with SO [Atkins et al., 2014]. Moreover, some studies that used the ratio between muscle and fat mass index (Muscle-to-fat ratio or visceral fat area-to-thigh muscle area ratio) as an index of SO consistently reported a positive association between SO and CMD risk [Lim et al., 2010a; Kim et al., 2011]

DYNAPENIA VERSUS SARCOPENIA FOR CARDIOMETABOLIC HEALTH

It was originally thought that sarcopenia largely contributed the dynapenia (age-related loss of muscle strength). However, recent data revealed that other physiological factors that are independent of loss of muscle mass plays a greater role in dynapenia [Clark and Manini, 2012]. In other words, dynapenia is distinct from sarcopenia. Therefore, European Working Group on Sarcopenia in Older People (EWGSOP) recommends using the presence of both low muscle mass and low muscle strength or performance for the diagnosis of sarcopenia [Cruz-Jentoft et al., 2010]. Muscle strength and cardiorespiratory fitness have an independent and joint inverse association with metabolic syndrome [Jurca et al., 2004]. As noted above, several cross-sectional studies showed that SO defined using low muscle strength was associated with high circulating levels of proinflammatory markers in elderly subjects [Schrager et al., 2007]. In addition, a prospective Cardiovascular Health Study found that

subjects with SO that was defined using muscle strength had an increased CVD risk than did those with SO that was defined using muscle mass [Stephen and Janssen, 2009]. Together, these results suggest that dynapenia might be more important for CMD risk than absolute or relative low muscle mass in elderly individuals.

AGE, SEX, NUTRITION, AND EXERCISE

Body composition continuously changes with aging. Specifically, muscle mass and strength decreases, whereas fat mass increases. Hence, older individuals tend to have a greater proportion of fat than younger people, despite having the same BMI. Furthermore, fat distribution changes with aging, and an increase in visceral fat mass might accelerate CMD risk. In samples of 89 male aged 30–42 years and 75 premenopausal females aged 23–50 years, males had increased visceral adipose tissue than female after adjusting for total fat mass [Lemieux et al., 1993]. In females, increased visceral fat is observed during the menopausal transition. CVD risk also may dramatically increase in women after menopause. CVD risk also increases dramatically in females after the menopause. There might be important differences in the effects of SO on CVD risk and mortality according to age and gender. One study reported that sarcopenia that was defined by mid-thigh muscle cross-sectional area divided by weight, was significant and negatively associated with arterial stiffness after adjusting for age and body height in males, but not in females [Ochi et al., 2010]. The author suggested that testosterone might underlie the gender-dependent association between sarcopenia and arterial stiffness. Another study showed that, although females (mean age, 71.1 ± 0.34 years) had a lower prevalence of sarcopenia and SO, as classified using skeletal muscle mass adjusted by height squared, their mortality risk was higher than that of males [Batsis et al., 2014]. Elderly females have more fat and less absolute skeletal muscle mass than elderly males and young individuals. Therefore, elderly females might have a higher risk of developing obesity and disabilities, which result in an increased risk of CMD and all-cause mortality. In older obese individuals, it is likely that regular resistance exercise combined with a slight reduction in calorie intake and adequate protein intake could help maintain optimal body composition [Marzetti et al., 2009; Stephen and Janssen, 2009]. Especially, in light of current findings regarding the association between dynapenia and CVD [Stephen and Janssen, 2009], interventions should ideally focus on simultaneously increasing muscle strength and decreasing visceral fat in elderly individuals with SO. Future studies will be needed to identify the best diet and type of exercise for SO and CMD in the elderly and also investigate whether diet alone, exercise alone, or combination of exercise, and diet represent the safest and most efficient strategy for delaying or reversing the progression from SO to CMD.

CONCLUSIONS AND FUTURE DIRECTIONS

This review suggests that the effect of low muscle mass and visceral obesity on CMD could be explained by a vicious cycle between loss of muscle, reduced strength and the accumulation of visceral fat via the complex interrelationship between factors including proinflammatory cytokines, insulin resistance, oxidative stress, mitochondrial dysfunction, hormonal imbalance, dietary caloric surplus, and low physical activity. In addition, recent clinical observational studies suggested that SO might be associated with CMD and mortality, although these findings should be confirmed in future studies.

SO is a growing public healthcare problem because of the rapid expansion of the elderly population, the obesity epidemic, and a lack of solution to this problem. Moreover, SO is more complicated than either sarcopenia or obesity alone, because it is not just the simple combination of sarcopenia and obesity. Although several health consequences of sarcopenia and obesity have been determined, information regarding the association between SO and CMD is relatively limited. Recently, given the critical importance of SO to cardiometabolic health, there is the need to encourage researchers to undertake basic and clinical studies to assess the association between SO and CMD in a variety of settings: in epidemiological studies, where little attention has previously focused on muscle qualities such as strength; in prospective studies; and in therapeutic intervention studies aimed at improving strength or physical performance and simultaneously reducing abdominal fat in the elderly. To this end, establishing a unified definitions of SO and standardized primary outcomes for SO are required.

Although the pathophysiology behind the relationship between SO and CMD has not been explored completely, it is likely that effect of SO on CMD might be explained partly by the secretion of adipokines from abdominal fat or ectopic fat and myokines from skeletal muscle. When visceral fat has accumulated, the imbalance of adipokines contributes to the development of cardiovascular and metabolic diseases. In contrast, skeletal muscle might secrete myokines to confer some of the protective properties of exercise [Pedersen and Febbraio, 2012]. As such, these myokines would oppose the harmful effects of pro-inflammatory adipokines secreted from visceral adipose tissue [Pedersen and Febbraio, 2012]. Therefore, SO seem to be crucial for understanding the connection between fat mass gain and loss of muscle.

SO and CMD likely interact with each other and share common pathologic processes such as inflammation, oxidative stress, and insulin resistance. There are strong theoretical reasons that SO will be a predictor of CVD. The evidence available in support of this hypothesis has been starting to emerge, although further research is still required. Improving our understanding of the concept of SO might be helpful for alleviating the global threat of SO in the aging society.

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